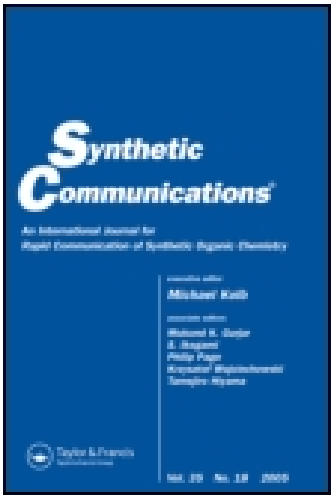

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Strategies towards the Synthesis of 6-N,N-Diethylcarbamyloxy-1,4-dimethoxy-7-naphthylboronic Acid

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Strategies towards the Synthesis of 6-*N*,*N*-Diethylcarbamyloxy-1,4-dimethoxy-7-naphthylboronic Acid

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Abstract: After acetylation, condensation between Danishefsky's diene and benzoquinone afforded a stable methoxytriacetoxydihydronaphthalene intermediate, which was subsequently transformed by the Snieckus DOM protocol into the regiospecific 7-naphthylboronic acid.

Keywords: boronic acids, carbamate esters, Danishefsky's diene, Snieckus DOM

Numerous binaphthoquinones (viz., diospyrin **1** and isodiospyrin **2**) have been isolated from plant sources (viz., Diospyros piscatoria (Gurke),)[1] *Diospyros montana*,[2] and *Diospyros rotandifolia*)[2,3] and have formed a common ingredient in several medicinal decoctions. The importance of diospyrin **1** and some

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of its analogs as an antimycobacterial agent has recently been published,[4] and it was previously synthesized by Mori and Yoshida[5] (Fig. 1). In Asian countries, other binaphthoquinones (viz., 3,3′-biplumbagin **3**, elliptinone **4**, and maritinone **5**) have been isolated from *Plumbago zeylancia* and also used in medicinal applications.[6]

Within the limited examples in Fig. 1, the linkage between the two naphthoquinones falls within one of three categories (viz., quinone–quinone **3**, quinone–nonquinone **1**, and nonquinone–nonquinone **2**, **4**, and **5**). This linkage has a profound effect on the degree and nature of the activity of these systems,[1] and it would appear that the hydroxy groups also have an important role to play. To make a contribution to the range of binaphthoquinones and their activity, the naphthylboronic acid **27** was required for Suzuki cross-coupling reactions. This article describes some of the chemistry that led to its synthesis.

The route envisaged for the synthesis of the key intermediate phenol **12** required the condensation between Danishefsky's diene **6** and quinone **7**.[7] Subjection of the crude reaction mixture to chromatographic purification afforded the quinone **8**[8] in a yield of 40%. Acetylation of the 6-OH group

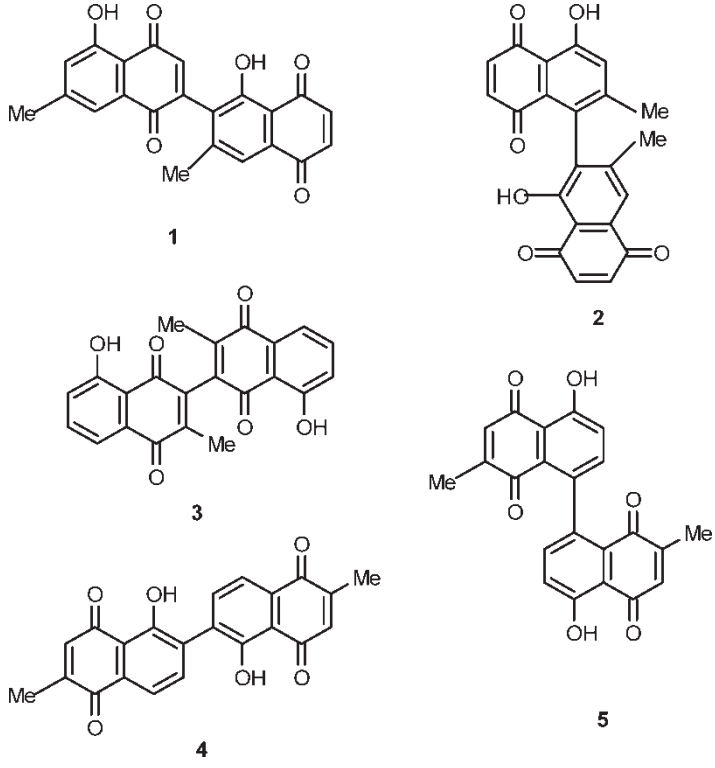


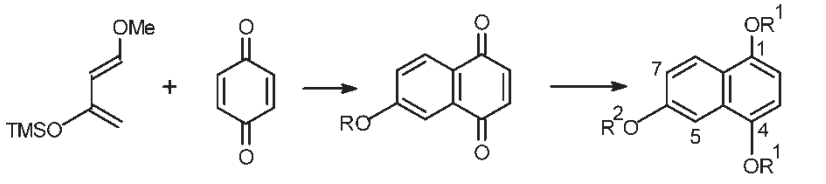
Figure 1. Biologically active binaphthoquinones.

with acetic anhydride in pyridine afforded a quantitative yield of the corresponding acetate **9**.[9] This compound was subsequently reductively methylated by reducing the quinone with aqueous sodium dithionite[9] first, followed by treatment with dimethylsulphate and potassium carbonate in refluxing acetone. However, the major product isolated from the reaction mixture was the trimethoxy naphthalene **10** (71%) with the desired product **11** being obtained in 22% yield. No doubt, under the basic reaction conditions employed, the acetate group at C-6 was hydrolyzed to the corresponding phenol, which in turn was methylated. This problem was overcome by methylation under neutral conditions in benzene using methyl iodide and silver(I) oxide[10] to afford the desired naphthalene acetate **11** in 90% yield from **9**. Finally, gentle hydrolysis of acetate **11** using 1% KOH/MeOH led to the isolation of the target molecule **12**[11] in a yield of 88% (Scheme 1).

To improve the overall yield of naphthol **12,** due to the poor yield in the formation of quinone **8**, an alternative route was investigated. Contrary to Danishefsky's reported findings,[7] in our hands, acetylation of the crude Diels–Alder reaction mixture afforded only an 8% yield of the 1,4,6-triacetoxynaphthalene **13**.[7] The major product isolated in a 92% yield was the fairly stable enol acetate **14** (Fig. 2). Assignment of the structure **14** to the enol acetate is based on data from HRMS, ^{1}H NMR, and ^{13}C NMR spectra.

Our initial attempt to aromatize the adduct **14** into the desired triacetate **13** involved its treatment with acetic anhydride and pyridine under reflux. However, careful chromatographic purification of the reaction mixture afforded three products [viz., the triacetoxynaphthalene **13** (42%), the tetraacetoxybinaphthyl ether **15** (11%), and surprisingly, the diacetoxynaphthol **16** (21%) (Fig. 3)]. Assignment of the structure **15** to the binaphthyl ether was based on HRMS, IR, and ^{1}H and ^{13}C spectral data.

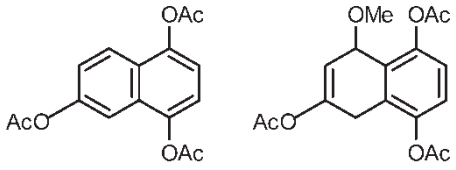
Heating adduct **14** in acetic acid under reflux effected a quantitative conversion into the desired triacetoxynaphthalene **13**. Finally, treatment of **13** with cerium ammonium nitrate in aqueous acetonitrile afforded a quantitative yield of acetoxyquinone **9**. Thus the latter route (viz., **14** > **13** > **9** > **11** > **12**), which involved five steps with an overall yield of 73%, was preferred



6 **7** **8** R = OH, **9** R = Ac

10 $R^1 = R^2$ = Me
11 R^1 = Me; R^2 = Ac
12 R^1 = Me; R^2 = H

Scheme 1.



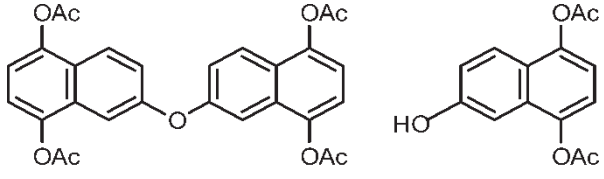
13 14

Figure 2. Acetylation products of the Diels–Alder adduct.

over the earlier route (**8** > **9** > **11**> **12**), which involved four steps but had an overall yield of 32%.

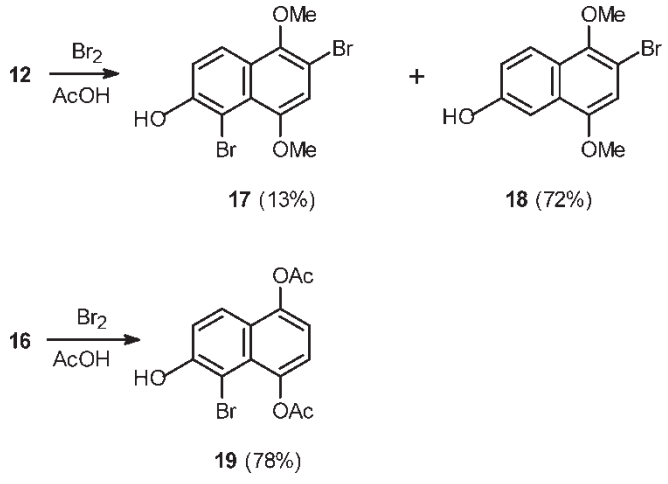
BROMINATIONS

The original route envisaged for the synthesis of the target naphthalene boronic acid **27** required the regiospecific bromination[12] at position 7 in phenol **12** (see numbering in Scheme 1) followed by protection of the C-6 OH group, metal–halogen exchange, and boronation.[13] Thus treatment of naphthol **12** with 1 mol equivalent of bromine in acetic acid produced two products [viz., the dibromophenol **17** (13%) and the monobromophenol **18** (72%) (Scheme 2)]. This result demonstrated two features: (a) that the two methoxy groups activated the ring of their attachment to a greater extent than the 6-OH and (b) that α-activation of the 6-OH was more strongly directed at C-5 than at C-7. To evaluate the influence that reversing the electron-donating character at C-1 and C-4 of phenol **12** would have on the bromination products, diacetoxy phenol **16** was brominated in a similar way. However, only the monobrominated diacetoxyphenol **19** was isolated (78%). Thus although bromination occurred exclusively in the phenol ring in this case, α-naphthalene activation controlled attack at the sterically more congested C-5 site to override β-naphthalene activation at the sterically more accessible C-7 position.



15 16

Figure 3. Conversion products of **14**.



Scheme 2.

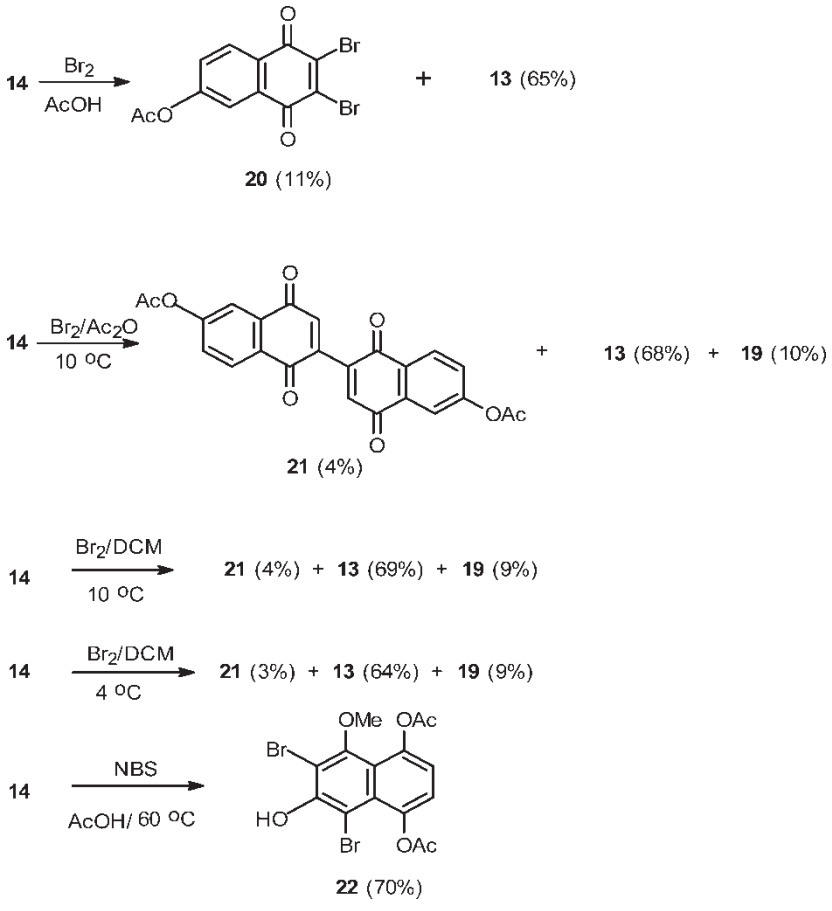
Attention was then focused on bromination of adduct **14**. With its olefinic bond between C-6 and C-7, it was hoped to eventually afford the C-7 halogenated products. Thus treatment of adduct **14** with 1 mol equivalent of bromine in acetic acid at 24°C for 3 h afforded the 2,3-dibromonaphthoquinone **20** (11%) and triacetoxynaphthalene **13** (65%) as the only two identifiable products (Scheme 3).

On the other hand, treatment of adduct **14** with 1 mol equivalent of bromine in acetic anhydride at 10°C afforded three products [viz., the bis-naphthoquinone **21** (4%), the triacetoxynaphthalene **13** (68%), and the bromophenol **19** (10%)].

Changing the solvent to dichloromethane did not alter the product distribution nor the yields to any extent. Thus at 10°C the products isolated were **21** (4%), **13** (69%), and **19** (10%), whereas at 4°C, the isolated products were **21** (3%), **13** (64%), and **19** (9%). Finally, treatment of adduct **14** with 5 mol equivalents of NBS in hot acetic acid produced the dibromophenol **22** in a yield of 71% (Scheme 3).

BORATIONS

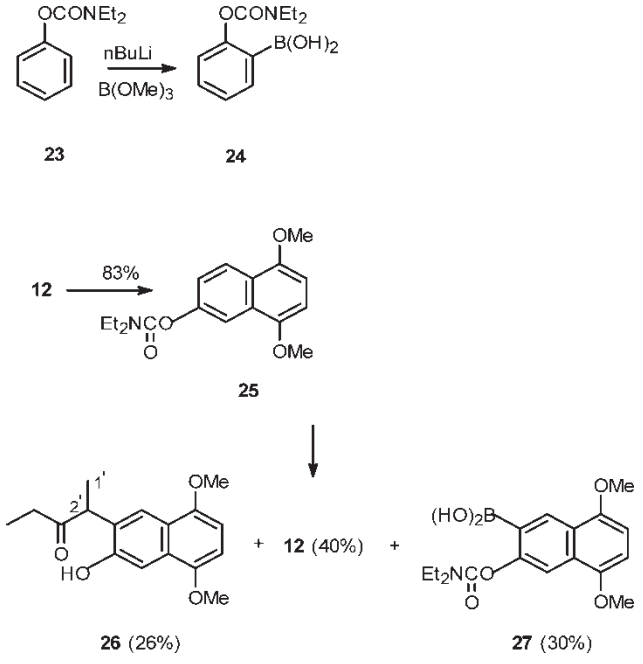
As a consequence of the bromination strategy not being able to regioselectively brominate C-7 of naphthol **12**, an entirely new approach was adopted [viz., employing the well-proven directed ortho metallations (DOM) developed over the years by Snieckus.[13,14] Thus to establish the methodology, phenol was converted to the carbamate **23** (94%)[15] and subsequently to the *ortho*-boronic acid **24** (82%)[13] (Scheme 4). Similarly, phenol **12** was



Scheme 3.

converted into the corresponding carbamate **25** (83%), which upon treatment under a similar protocol consistently afforded three products, which were chromatographically separated. The first product to elute was assigned the structure **26** (26%), and the next was the naphthol **12** (40%), a product of hydrolysis. The last compound to elute was the target boronic acid **27** (30%).

Assignment of the structure **26** to the first product to elute was based on the following spectral evidence. The molecular ion at m/z 288.1346 confirmed a molecular formula of $C_{17}H_{20}O_4$ (requires 288.1362). In addition, a major fragmentation representing the loss of a CH_3CH_2CO-group (viz., m/z 57) supports the assigned structure as well. Strong absorption bands in the infrared spectrum at 3383 and 1680 cm^{-1} supported the presence of hydroxy and ketone functional groups respectively. A 3-proton triplet at



Scheme 4.

0.97 ppm (*J* 7.4) in the ^{1}H NMR spectrum was demonstrated via correlation spectroscopy (COSY) coupling to two 1-proton dt's at 1.60 and 1.90 ppm (*J* 18.0 and 7.4) and represents H-5′ and H-4′ of the pentanoyl side chain. A 3-proton doublet at 1.29 ppm (*J* 7.0) assigned to H-1′ was also confirmed via COSY spectroscopy to be coupled to a 1-proton quartet at 3.74 ppm (*J* 7.0) assigned to H-2′ of the side chain. In the aromatic region, two *ortho*-coupled 1-proton doublets at 6.50 and 6.73 ppm (*J* 8.0) are assigned to H-2 and H-3 respectively, whereas two 1-proton singlets at 7.63 and 8.80 ppm are assigned to H-5 and H-8 respectively. A D_2O exchangeable peak at 12.00 ppm is assigned to the C-6-OH group. Significant signals in the ^{13}C NMR spectrum include those at 11.9 and 17.6 ppm for C-5′ and C-1′, 27.3 and 41.9 ppm for C-4′ and C-2′, and 211.5 for the C-3′ C═O.

Assignment of the position of boronation for boronic acid **27** was based primarily on the four 1-proton signals in the aromatic region of the ^{1}H NMR spectrum [viz., a doublet at 6.53 ppm (*J* 7.0) assigned to H-2, a doublet at 6.70 ppm (*J* 7.0) assigned to H-3, a singlet at 7.67 ppm assigned to H-5, and a singlet at 8.23 ppm assigned to H-8].

Thus, the target boronic acid **27** was synthesized in a overall yield of 18% involving seven steps starting from Danishefsky's diene **6** and quinone **7**. Attention is currently being focused on improving the yield of the sterically

preferred *ortho*-directed boronation of carbamate **25** and its subsequent reactions in Suzuki–Mayori cross-coupling protocols.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded using a Varian 200-MHz spectrometer at 20°C in deuterochloroform and ***J*** values are given in Hertz. Infrared spectra were measured as Nujol mulls on a Perkin Elmer FT-IR 1000PC spectrometer. Melting points were recorded using a Fisher-Johns melting-point apparatus. Mass spectra were recorded on a Finnigan-Matt GCQ spectrometer. Column chromatography was carried out using Merck Kieselgel 60 (70–230 mesh) as dry columns. The residue obtained upon workup refers to material obtained from the dried (magnesium sulphate) organic extract after filtration and solvent removal. Hexane refers to that fraction of bp 70–75°C. In ^{13}C-spectra, assignments with the same superscript may be interchanged.

6-Hydroxy-1,4-naphthoquinone (8)

Treatment of benzoquinone **7** (3.0 g, 27.8 mmol) in benzene (60 mL) with 1-methoxy-3-trimethylsilyloxybutadiene **6** (5.0 g, 29.2 mmol)[7] in benzene (10 mL) dropwise over 5 min followed by heating under reflux for 3 h and evaporation of solvent afforded a residue that was chromatographed using EtOAc–hexane (3:7) to afford quinone **8** (1.92 g, 40%) as yellow crystals, mp 194–196°C (from EtOAc–hexane). (Lit.[8] mp 193–194°C); ν_{max} 3450 and 1666 cm^{-1}; δ_H [$(CD_3)_2CO$] 6.96 (2H, s, H-2 and H-3), 7.25 (1H, dd, *J* 8.8 and 2.6, H-7), 7.42 (1H, d, *J* 2.6, H-5) and 7.94 (1H, d, *J* 8.8, H-8). δ_C 112.8 (C-7), 121.7 (C-5)[a], 125.9 (C-4a)[b], 129.9 (C-8)[a], 135.3 (C-8a)[b], 139.2 (C-2)[c], 140.0 (C-3)[c], 163.6 (C-6), 184.6 and 185.8 (C=O). (Found: C, 69.20; H, 3.3%; *M*, 174. Calc. for $C_{10}H_6O_3$: C, 69.0; H, 3.5%; *M*, 174.)

6-Acetoxy-1,4-naphthoquinone (9)

Hydroxyquinone **8** (348 mg, 2.0 mmol) in acetic anhydride (15 mL) and pyridine (2 mL) was stirred under nitrogen at 24°C for 18 h after which the reaction solution was poured into ice/water to give a precipitate of the acetoxyquinone **9** (430 mg, 100%) as yellow needles, mp 98–99°C (from EtOAc–hexane) (Lit.[9] mp 96–97°C) ν_{max} 1727 and 1668 cm^{-1}; δ_H 2.36 (3H, s, CH_3CO), 6.99 (2H, s, H-2 and H-3), 7.48 (1H, dd, *J* 8.4 and 2.5, H-7), 7.80 (1H, d, J 2.5, H-5) and 8.13 (1H, d, *J* 8.4, H-8). δ_C 21.1 (CH_3CO_2), 119.6 (C-7), 127.3 (C-5)[a], 128.6 (C-8)[a], 129.6 (C-8a)[b], 133.7 (C-4a)[b], 138.7 (C-2)[c], 138.9 (C-3)[c], 155.2 (C-6), 168.5 (C=O ester), 184.1

and 184.2 (C═O of quinone). (Found: C, 66.6; H, 3.5%; *M*, 216. Calc. for $C_{12}H_8O_4$: C, 66.7; H, 3.7%; *M*, 216.)

1,4,6-Trimethoxynaphthalene (10) and 6-Acetoxy-1,4-dimethoxynaphthalene (11)

6-Acetoxy-1,4-naphthoquinone **9** (300 mg, 1.39 mmol) in ether (200 mL) was vigorously shaken with sodium dithionite solution (10 g/100 mL), which resulted in the ethereal solution losing its yellow color. The ether solution was dried ($MgSO_4$) and evaporated to yield a residue, which was immediately dissolved in acetone (20 mL) and treated with Me_2SO_4 (700 mg, 5.56 mmol) in the presence of K_2CO_3 (770 mg, 5.56 mmol) and then vigorously stirred and heated under reflux under an N_2 atmosphere for 12 h. The filtrate was concentrated under reduced pressure and purified by column chromatography using EtOAc–hexane (1:4) as eluent to afford **10** (213 mg; 71%) as a yellow-brown oil; δ_H 3.99 (9H, s, 3x OCH_3), 6.57 (1H, d, *J* 8.4, H-2), 6.70 (1H, d, *J* 8.4, H-3), 7.17 (1H, dd, *J* 8.4 and 2.6, H-7), 7.51 (1H, d, *J* 2.6, H-5), 8.12 (1H, d, *J* 8.4, H-8). δ_C 55.4, 55.7 and 55.8 (OCH_3), 100.5 (C-2)[a], 101.2 (C-3)[a], 104.2 (C-7)[a], 118.1 (C-5)[b], 121.6 (C-4a)[c], 123.7 (C-8)[b], 127.6 (C-8a)[c], 148.8 (C-1)[d], 149.9 (C-4)[d], and 158.1 (C-6). (Found: C, 71.3; H, 6.6%; *M*, 218. Calc. for $C_{13}H_{14}O_3$: C, 71.5; H, 6.5%; *M* 218.)

Further elution afforded 6-acetoxy-1,4-dimethoxynaphthalene **11** (66 mg, 22%) as a light yellow oil spectroscopically identical to the material synthesized as described next.

6-Acetoxy-1,4-dimethoxynaphthalene (11)

6-Acetoxyquinone **9** (500 mg, 2.3 mmol) in ether (200 mL) was similarly reduced as just described to afford a residue, which was immediately treated with methyl iodide (1.63 g, 11.5 mmol) in the presence of silver(II) oxide (1.45 g, 11.69 mmol) in dry benzene (40 mL). This was then stirred and heated under reflux under a nitrogen atmosphere for 12 h and filtered. The filtrate was concentrated under reduced pressure and purified by column chromatography using EtOAc–hexane (1:4) as eluent, to afford the acetoxynaphthalene **11** (509 mg, 90%) as a light yellow oil; ν_{max} 1726 cm^{-1}; δ_H 2.35 (3H, s, $OCOCH_3$), 3.93 (6H, s, 2x OCH_3), 6.66 (1H, d, *J* 9.2, H-2), 6.68 (1H, d, *J* 9.2, H-3), 7.30 (1H, dd, *J* 9.2 and 2.6, H-7), 7.95 (1H, d, *J* 2.6, H-5), and 8.25 (1H, d, *J* 9.2, H-8). δ_C 21.1 (CH_3CO_2), 55.7 (OCH_3), 55.8 (OCH_3), 103.2 (C-2)[a], 104.2 (C-3)[a], 113.3 (C-7), 120.8 (C-5)[b], 123.7 (C-8)[b], 124.4 (C-4a)[c], 127.1 (C-8a)[c], 148.8 (C-4)[d], 149.2 (C-1)[d], 149.6 (C-6), 169.6 (C═O). (Found: C, 68.6; H, 5.5%; *M*, 246. Calc. for $C_{14}H_{14}O_4$: C, 68.3, H, 5.7%; *M*, 246.)

6-Hydroxy-1,4-dimethoxynaphthalene (12)

6-Acetoxy-1,4-dimethoxynaphthalene **11** (130 mg, 0.53 mmol) in MeOH (10 mL) was treated with 1% KOH/MeOH (1.1 mL) with constant stirring at 24°C for 1 h. The reaction mixture was then poured into water (100 mL) and acidified (litmus) with 0.1 M HCl, and the solution was extracted with dichloromethane to give naphthol **12** (95 mg, 88%) as a greenish oil; ν_{max} 3368 cm^{-1}; δ_H 3.93 (6H, s, 2x CH_3O), 5.34 (1H, s, D_2O exchangeable, 6-OH), 6.55 (1H, d, *J* 8.0, H-2), 6.70 (1H, d, *J* 8.0, H-3), 7.20 (1H, dd, *J* 8.0 and 2.4, H-7), 7.51 (1H, d, *J* 2.4, H-5) and 8.25 (1H, d, *J* 8.0, H-8). δ_C 55.8 (OCH_3), 55.9 (OCH_3), 101.1 (C-5)[a], 104.4 (C-2)[a], 104.5 (C-3)[a], 117.2 (C-7)[a], 121.7 (C-8a)[b], 124.2 (C-8), 127.8 (C-4a)[b], 148.6 (C-1)[c], 150.0 (C-4)[c], 154.0 (C-6). (Found: C, 70.7; H, 5.7%; *M*, 204. Calc. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9%; *M*, 204.)

1,4,7-Triacetoxy-5-methoxy-5,8-dihydronaphthalene (14)

Benzoquinone **7** (3.0 g, 27.8 mmol) in benzene (60 mL) was treated with 1-methoxy-3-trimethylsilyloxybutadiene **6** (5.0 g, 29.2 mmol) in benzene (10 mL) at 24°C, and the resulting solution was gently heated and stirred at 60–70°C for 1 h under nitrogen. The residue obtained upon removal of the solvent was treated with acetic anhydride (80 mL) and pyridine (40 mL) at 25°C for 12 h and then poured into water (400 mL) and chilled. The product was chromatographed using EtOAc–hexane (3:7) as eluent to afford the triacetate **14** (8.54 g, 92%) as white crystals, mp 146–147°C (from EtOH); ν_{max} 1728 cm^{-1}; δ_H 2.20, 2.32, and 2.33 (each 3H, each s, CH_3CO_2-), 2.66 (1H, dd, *J* 17.8 and 2.1, *pseudo* H-8a), 2.91 (1H, ddd, *J* 17.8, 5.0, and 2.4, *pseudo* H-8e), 3.23 (3H, s, 5-CH_3O), 4.57 (1H, dd, *J* 5.0 and 2.2, H-5), 6.39 (1H, d, *J* 2.4, H-6), 6.99 (1H, d, *J* 8.8, H-2), and 7.10 (1H, d, *J* 8.8, H-3). δ_C 20.9, 21.0, and 21.2 (3x CH_3CO), 32.4 (C-8), 55.5 (CH_3O), 69.9 (C-5), 106.8 (C-6), 121.3 (C-2)[a], 123.5 (C-3)[a], 123.9 (C-4a)[b], 127.2 (C-8a)[b], 144.1 (C-1)[c], 146.4 (C-7)[c], 150.2 (C-4)[c], 168.5, 168.9, and 169.0 (C═O). (Found: C, 61.3; H, 5.6%; *M*, 334. Calc. for $C_{17}H_{18}O_7$: C, 61.1; H, 5.4%; *M*, 334.) Further elution afforded the 1,4,6-triacetoxynaphthalene **13** (67 mg, 8%) identical to material synthesized as described next.

1,4,6-Triacetoxynaphthalene (13), 1,1′4,4′-Tetraacetoxy-6,6′-oxobisnaphthalene (15), and 1,4-Diacetoxy-6-hydroxynaphthalene (16)

Adduct **14** (480 mg, 1.44 mmol) in acetic anhydride (25 mL) and pyridine (5 mL) was heated and stirred under reflux for 2 h; the reaction mixture then poured into water (100 mL) and extracted with dichloromethane,

which was backwashed with water, 0.5 M hydrochloric acid, and finally 10% aqueous sodium hydrogen carbonate. The residue obtained upon workup was very carefully chromatographed using EtOAc–hexane (3:7) as eluent to afford in order of elution the 1,4,6-triacetoxynaphthalene **13** (183 mg, 42%) as cream crystals, mp 106–107°C (from ethanol). (Lit.[15] mp 94–95°C); ν_{max} 1726 cm^{-1}; δ_H 2.34 and 2.4(×2) (9H, s, CH_3CO_2), 7.24 (1H, d, *J* 8.4, H-2), 7.25 (1H, d, *J* 8.4, H-3), 7.32 (1H, dd, *J* 9.2 and 2.2, H-7), 7.61 (1H, dd, *J* 2.2 and 0.8, H-5), and 7.91 (1H, dd, *J* 9.2 and 0.2, H-8). δ_C 21.1(×2), 21.3 (CH_3CO_2), 112.9 (C-7)[a], 117.6 (C-5)[a], 118.7 (C-8)[a], 122.5 (C-2)[a], 123.5 (C-3)[a], 125.7 (C-4a)[b], 128.4 (C-8a)[b], 144.1 (C-1)[c], 144.4 (C-4)[c], 149.6 (C-1)[c], 169.1, 169.2, and 169.3 (C═O). (Found: C, 63.4; H, 4.5%; *M*, 302. Calc. for $C_{16}H_{14}O_6$: C, 63.4; H, 4.5%; *M*, 302.)

Further elution afforded the binaphthalene ether **15** (80 mg, 11%) as light yellow crystals, mp 123–124°C (from EtOAc–hexane); ν_{max} 1740–1750 cm^{-1}; δ_H 2.36 and 2.44 (each 6H, s, CH_3CO_2), 6.40 (1H, d, *J* 8.5, H-2′)[a], 6.44 (1H, d, *J* 8.5, H-3′)[a], 6.85 (d, *J* 8.2, H-2)[a], 6.94 (1H, d, *J* 8.2, H-3)[a], 7.16 (1H, dd, *J* 9.0 and 2.2, H-7)[b], 7.22 (1H, dd, *J* 8.8 and 2.4, H-7′)[b], 7.42 (1H, d, *J* 2.2, H-5)[c], 7.74 (1H, d, *J* 8.8, H-8′)[d], 7.75 (1H, d, *J* 2.4, H-5′)[c], and 8.02 (1H, d, *J* 9.0, H-8)[d]. δ_C 21.0, 21.1, 21.2, and 21.3 (4x CH_3CO_2), 107.8, 108.6, 112.1, 114.1, 117.9, 119.1, 120.7, 122.0, 122.7, and 123.3 (C-H aryl), 124.6, 125.5, 125.9, and 128.1 (C-4a, C-8a, C-4a′, and C-8a′), 139.4 and 139.7 (C-6 and C-6′), 148.2, 149.5, 149.8, and 150.1 (C-1, C-4, C-1′, and C-4′), 169.9, 170.2, 170.6, and 170.7 (C═O). (HRMS: 502.1260. Calc. for $C_{28}H_{22}O_9$: 502:1264.)

Further elution afforded a thick oil, which solidified on standing to give 1,4-diacetoxy-6-hydroxynaphthalene **16** (80 mg, 21%) as white needles, mp 141–142°C (from EtOAc–hexane); ν_{max} 3350 and 1729 cm^{-1}; δ_H 2.41 and 2.45 (each 3H, s, CH_3CO_2), 5.60 (1H, br s, D_2O exchangeable, 6-OH,), 7.02 (1H, dd, *J* 8.2 and 2.6, H-7), 7.06 (1H, dd, *J* 2.6 and 0.6, H-5), 7.06 (1H, d, *J* 8.2, H-2), 7.19 (1H, d, *J* 8.2, H-3), and 7.71 (1H, dd, *J* 8.4 and 0.6, H-8). δ_C 21.0 and 21.1 (CH_3CO_2), 104.0 (C-7), 115.2 (C-5)[a], 118.5 (C-8)[a], 119.1 (C-2)[a], 123.1 (C-4a)[b], 123.9 (C-3)[a], 129.2 (C-8a)[b], 143.3 (C-1)[c], 144.7 (C-4)[c], 154.7 (C-6), 169.6 and 169.7 (C═O). (Found: C, 64.6; H, 4.5%; *M*, 260. Calc. for $C_{14}H_{12}O_5$: C, 64.4; H, 4.65%; *M*, 260.)

1,4,6-Triacetoxynaphthalene (13)

Adduct **14** (500 mg, 1.5 mmol) in acetic acid (20 mL) was heated under reflux for 2 h, after which the mixture was poured into water (200 mL) and cooled to 0°C for 12 h. The precipitate that formed was filtered off to afford 1,4,6-triacetoxynaphthalene **13** (453 mg, 100%), spectroscopically identical to the material synthesized earlier.

6-Acetoxy-1,4-naphthoquinone (9)

To the triacetoxynaphthalene **13** (520 mg, 1.72 mmol) in CH_3CN (30 mL) and water (6 mL), cerium(IV) ammonium nitrate (4.71 g; 5 mmol) in water (6 mL) was added with rapid stirring at 24°C. Stirring was continued for 3 h, after which the reaction mixture was poured into water (100 mL) to give the quinone **9** (372 mg, 100%), identical to material prepared earlier.

2,5-Dibromo-6-hydroxy-1,4-dimethoxynaphthalene (17) and 2-Bromo-6-hydroxy-1,4-dimethoxynaphthalene (18)

6-Hydroxy-1,4-dimethoxynaphthalene **12** (110 mg, 0.54 mmol) in AcOH (10 mL) was treated with bromine (100 mg, 0.54 mmol) in AcOH (2 mL) with constant stirring for 15 min, after which the reaction mixture was poured into water (100 mL), extracted with dichloromethane, and backwashed with 10% aqueous sodium hydrogen carbonate to afford a residue, which was purified by column chromatography using EtOAc–hexane (3:7) as eluent to give dibromonaphthol **17** (25 mg, 13%) as yellow crystals, mp 79–80°C (from EtOAc–hexane); ν_{max} 3350 cm^{-1}; δ_H 3.90 (6H, s, CH_3O), 6.51 (1H, s, D_2O exchangeable, 6-OH), 6.96 (1H, s, H-3), 7.30 (1H, d, *J* 9.2, H-7), 8.00 (1H, d, *J* 9.2, H-8). δ_C 56.3 and 61.6 (CH_3O), 102.2 (C-2), 109.8 (C-5)[a], 112.3 (C-3)[a], 117.9 (C-7)[b], 123.9 (C-8)[b], 124.2 (C-8a)[c], 126.5 (C-4a)[c], 147.3 (C-6), 151.4 (C-1)[d], 151.8 (C-4)[d]. [Found: C, 40.0; H, 2.8%; *M*, 360/362/364 (1:2:1). Calc. for $C_{12}H_{10}Br_2O_3$: C, 39.8; H, 2.8%; *M*, 360/362/364 (1:2:1).]

Further elution afforded the 2-bromonaphthalene **18** (112 mg, 72%) as light yellow needles, mp 108–109°C (from EtOAc–hexane); ν_{max} 3350 cm^{-1}; δ_H 3.93 (6H, s, CH_3O), 5.25 (1H, s, D_2O exchangeable, 6-OH), 6.84 (1H, s, H-3), 7.15 (1H, dd, *J* 8.4 and 2.4, H-7), 7.48 (1H, d, *J* 2.4, H-5), 7.99 (1H, d, *J* 8.4, H-8). δ_C 56.0 (OCH_3), 61.6 (OCH_3), 105.3 (C-2), 108.8 (C-7)[a], 109.1 (C-3)[a], 118.8 (C-5)[a], 124.3 (C-8)[a], 124.4 (C-4a)[b], 127.3 (C-8a)[b], 147.1 (C-6), 151.3 (C-1)[c], 153.9 (C-4)[c]. [Found: C, 50.7; H, 3.6%; *M*, 282/284 (1:1). Calc. for $C_{12}H_{11}BrO_3$: C, 50.9; H, 3.9%; *M*, 282/284 (1:1).]

1,4-Diacetoxy-5-bromo-6-hydroxynaphthalene (19)

Diacetoxynaphthol **16** (260 mg, 1.0 mmol) in AcOH (15 mL) was treated with bromine (160 mg, 1.0 mmol) in AcOH (4 mL) with stirring at 24°C, and stirring was continued for 20 min, after which time the reaction mixture was poured into ice/water (100 mL) to produce 5-bromophenol **19** (264 mg, 78%) as slightly greyish crystals, mp 127–128°C (from EtOAc–hexane); ν_{max} 3350 and 1740 cm^{-1}; δ_H 2.46 (6-H, s, $COCH_3$), 6.48 (1H, s, D_2O exchangeable, 6-OH), 7.15 (1H, d, *J* 8.2, H-2), 7.21 (1H, d, *J* 8.2, H-3),

7.28 (1H, d, *J* 9.2, H-7), and 7.83 (1H, d, *J* 9.2, H-8). δ_C 21.1 (OCO*C*H_3), 22.0 (OCO*C*H_3), 100.4 (C-7), 116.5 (C-3)[a], 118.0 (C-5)[a], 122.1 (C-2)[a], 123.6 (C-8)[a], 124.8 (C-4a)[b], 126.1 (C-8a)[b], 142.3 (C-1)[c], 144.8 (C-4)[c], 152.4 (C-6), 169.1 (C═O), and 170.2 (C═O). [Found: C, 49.7; H, 3.3%; *M*, 338/340 (1:1). Calc. for $C_{14}H_{11}BrO_5$: C, 49.6, H, 3.3%; *M*, 338/340 (1:1).]

6-Acetoxy-2,3-dibromo-1,4-naphthoquinone (20)

Bromine (268 mg, 1.68 mmol) in acetic acid (2 mL) was dripped into a solution of adduct **14** (560 mg, 1.68 mmol) in acetic acid (8 mL) at 24°C over 3 min in a nitrogen atmosphere and thereafter stirring was continued for 3 h. The reaction mixture was poured into water (200 mL), and the organic material extracted into dichloromethane, which was backwashed with saturated sodium hydrogen carbonate to yield a residue, which was chromatographed using EtOAc–hexane (3:7) as eluent to yield the dibromonaphthoquinone **20** (70 mg, 11%) as bright yellow crystals, mp 181–182°C (from EtOAc–hexane); ν_{max} 1754 and 1665 cm^{-1}; δ_H 2.37 (3H, s, OCOCH_3), 7.52 (1H, dd, *J* 8.8 and 2.2, H-7), 7.90 (1H, d, *J* 2.2, H-5), and 8.23 (1H, d, *J* 8.8, H-8). δ_C 21.1 (OCOCH_3), 121.3 (C-7)[a], 127.9 (C-5)[a], 128.3 (C-2)[a], 130.3 (C-8)[a], 132.5 (C-3)[a], 142.4 (C-4a)[b], 143.0 (C-8a)[b], 155.6 (C-6), 168.3 (C═O of ester), 175.0 and 175.2 (C═O). (Found: C, 38.3; H, 1.5%; M^+, 372/374/376. Calc. for $C_{12}H_6Br_2O_4$: C, 38.5; H, 1.6%; *M* 372/374/376.) Further elution afforded 1,4,6-triacetoxynaphthalene **13** (330 mg, 65%), which had identical spectroscopic properties to the material synthesized previously.

6,6′-Diacetoxy-2,2′-binaphthoquinone (21), 1,4,6-Triacetoxynaphthalene (13), and 1,4-Diacetoxy-5-bromo-6-hydroxynaphthalene (19)

A solution of bromine (321 mg, 2.01 mmol) in acetic anhydride (2 mL) was dripped into a solution of the adduct **14** (670 mg, 2.01 mmol) in acetic anhydride (15 mL) under a nitrogen atmosphere at 10°C over 5 min, and stirring continued for 2 h. The reaction mixture was then poured into ice/water and extracted into dichloromethane. The residue obtained upon workup was chromatographed using EtOAc–hexane (3:7) to afford the dimer **21** (37 mg, 4%) as yellow crystals, mp 112–114°C (from EtOAc–hexane); ν_{max} 1728 and 1660 cm^{-1}; δ_H 2.36 (6H, s, OCOCH_3), 7.50 (4H, m, H-3, H-3′, H-7, and H-7), 7.79 and 7.87 (each 1H, each d, *J* 2.2, H-5 and H-5′), 8.11 and 8.20 (each 1H, each d, *J* 8.4, H-8 and H-8′). δ_C 21.1 (2x OCOCH_3), 120.0 (C-3)[a], 121.0 (C-3′)[a], 127.4 (C-7)[b], 127.4 (C-7′)[b], 128.5 (C-2)[c], 129.0 (C-5)[d], 129.3 (C-2′)[c], 130.0 (C-5′)[d], 132.6 (C-4a)[e], 133.5 (C-4a′)[e], 139.9 (C-8a)[e], 140.4 (C-8a′)[e], 140.5 (C-8 and C-8′)[e], 155.3 (C-6)[f], 155.6 (C-6′)[f], 168.3 and 168.4 (C═O of the two ester groups),

177.0, 177.3, 181.4, and 181.6 (C═O of quinones). (Found: C, 66.9; H, 3.1%; HRMS 430.0687. Calc. for $C_{24}H_{14}O_8$: C, 67.0; H, 3.3%; HRMS 430.0689.)

Further elution afforded 1,4,6-triacetoxynaphthalene **13** (413 mg, 68%), which had identical spectroscopic properties to the material synthesized earlier. Finally, the third compound to elute was the bromophenol **19** (68 mg, 10%) with identical spectral properties to material synthesized earlier.

1,4-Diacetoxy-5,7-dibromo-6-hydroxy-8-methoxy-naphthalene (22)

A solution of adduct **14** (500 mg, 1.50 mmol) dissolved in hot AcOH (30 mL) was added over 5 min to N-bromosuccinimide (2200 mg, 7.48 mmol) in AcOH (30 mL) and water (60 mL) at 55–60°C. The resulting solution was stirred at 55–60°C for 30–45 min, after which it was poured into ice/water, and the resulting precipitate was filtered to afford the dibromonaphthalene **22** (445 mg, 71%) as yellow crystals, mp 202–203°C (from EtOAc–hexane); ν_{max} 3400 and 1738 cm^{-1}; δ_H 2.44 and 2.50 (each 3H, s, OCOCH_3), 3.33 (3H, s, OCH_3), 5.09 (1H, s, D_2O exchangeable, 6-OH), 7.29 (1H, d, *J* 8.8, H-2), and 7.35 (1H, d, *J* 8.8, H-3). δ_C 21.1 and 21.7 (CH_3CO), 58.7 (MeO), 124.3 (C-5)[a], 125.1 (C-2)[a], 126.5 (C-7)[a], 126.9 (C-3)[a], 127.7 (C-4a)[b], 131.0 (C-8a)[b], 144.6 (2 ×) (C-1 and C-4)[c], 147.3 (x2) (C-6 and C-8)[c], 168.0 and 168.4 (C═O). (Found: C, 40.0; H, 2.5%; *M*, 446/448/450. Calc. for $C_{15}H_{12}Br_2O_6$: C, 40.2; H, 2.7%; M 446/448/450.)

N,*N*-Diethylphenylcarbamate (23)

Phenol (5 g, 53.19 mmol) in pyridine (10 mL) was treated with N,N-diethylcarbamylchloride (7.2 g, 53.10 mmol) in a pressure-capped glass bottle. This was then heated for 6 h in an oil bath at 110°C. The reaction mixture was then poured onto ice/water (200 mL) and extracted with ether, which was washed with 10% HCl followed by aqueous sodium hydrogen carbonate to afford the phenylcarbamate **23**[15] (9.14 g, 89%) as light brown oil; δ_H 1.22 (6H, m, C$H_3$$CH_2$-), 3.40 (4H, m, -C$H_2$$CH_3$), 7.0 to 7.5 (5H, m, Aryl-H).

2-*N*,*N*-Diethylcarbamyloxyphenyl Boronic Acid (24)

Phenylcarbamate **23** (1 g, 5.2 mmol) in THF (20 mL) was treated with TMEDA (600 mg, 5.2 mmol) followed by sec-butyllithium (5.5 mmol) at −78°C under a nitrogen atmosphere for 1 h and then allowed to warm to room temperature for 2 h. The reaction mixture was cooled again to −78°C for 40 min, treated with trimethylborate (540 mg, 5.2 mmol), stirred for a further 3 h, treated with saturated ammonium chloride (20 mL), and extracted with dichloromethane to afford the boronic acid **24**[14] (1.01 g,

82%) as a brown oil. δ_H 1.15 (6H, m, C*H*$_3$CH$_2$-), 3.25 (4H, m, CH$_3$C*H*$_2$-), 7.10 to 7.50 (3H, m, H-4, H-5, H-6), and 7.85 (1H, dd, *J* 9.2 and 2.6, H-3). (Found: C, 55.4; H, 6.5%; *M*, 237. Calc. for $C_{11}H_{16}BNO_4$: C, 55.7; H, 6.8%; *M*, 237.)

6-*N*,*N*-Diethylcarbamyloxy-1,4-dimethoxynaphthalene (25)

6-Hydroxy-1,4-dimethoxynaphthalene **12** (270 mg, 1.33 mmol) in pyridine (10 mL) was treated with N,N-diethylcarbamylchloride (180 mg, 1.33 mmol) in a pressure-capped glass bottle heated in an oil bath at 110°C for 3 h. The cooled reaction mixture was then poured into ice/water and extracted with ether. The ether solution was washed with 10% aqueous hydrochloric acid (20 mL) and then aqueous sodium hydrogen carbonate, and the residue obtained was purified by column chromatography using EtOAc–hexane (3:7) as eluent to afford carbamate **25** as an oil (334 mg; 83%); ν_{max} 1716 cm^{-1}; δ_H 1.26 (6H, m, 2x C*H*$_3$CH$_2$-), 3.20 (4H, m, -C*H*$_2$CH$_3$), 3.93 (6H, s, 2x OCH$_3$), 6.66 (1H, d, *J* 9.2, H-2), 6.68 (1H, d, *J* 9.2, H-3), 7.24 (1H, dd, *J* 9.2 and 2.4, H-7), 7.91 (1H, d, *J* 2.4, H-5), 8.20 (1H, d, *J* 9.2, H-8). δ_C 11.5 and 13.0 (*C*H$_3$CH$_2$-), 41.2 (x2) (-*C*H$_2$CH$_3$), 55.8 (x2, OCH$_3$), 102.8 (C-2)[a], 104.0 (C-3)[a], 113.2 (C-7), 121.4 (C-8)[b], 123.4 (C-5)[b], 124.1 (C-4a)[c], 127.2 (C-8a)[c], 149.3 (C-6)[d], 149.7 (C-4)[d], 149.8 (C-1)[d], 154 (C=O). (Found: C, 67.1, H, 7.2%; M^+, 303. Calc. $C_{17}H_{21}NO_4$: C, 67.3; H, 7.0%; *M*, 303).

6-Hydroxy-7-(2′-3′-oxapentyl)-1,4-dimethoxynaphthalene (26), 6-Hydroxy-1,4-dimethoxynaphthalene (12), and 6-*N*,*N*-Diethylcarbamyloxy-1,4-dimethoxy-7-naphthylboronic Acid (27)

To a stirred solution of sec-butyllithium (3 mol equiv.) and TMEDA (3M equiv.) in tetrahydrofuran (15 mL) at −78°C under nitrogen, the carbamate **25** (300 mg; 0.99 mmol) in tetrahydrofuran (3 mL) was added. After 1 h, MgBrEt$_2$O (780 mg, 3.03 mmol) was added with vigorous stirring. The reaction mixture was allowed to warm to 24°C and formed a clear solution, which was then cooled to −78°C, treated with methyl borate (310 mg, 3 mol), stirred at this temperature for 10 min, and then allowed to reach 24°C overnight. The resulting reaction mixture was poured into aqueous ammonium chloride and extracted with dichloromethane to yield an oily residue, which was chromatographed using EtOAc–hexane (3:7) as eluent to give as the first fraction the ketonaphthalene **26** (74 mg, 26%) as orange needles, mp 60–61°C (from EtOAc); ν_{max} 3383 and 1680 cm^{-1}; δ_H 0.97 (3H, t, *J* 7.4, H-5′), 1.29 (3H, d, *J* 7.0, H-1′), 1.60 (1H, dt *J* 18.0, 7.4, H-4′), 1.90 (1H, dt *J* 18.0, 7.4, H-4′), 3.74 (1H, q, *J* 7.0, H-2′), 3.93 and 3.97 (each 3H, s, CH$_3$O), 6.50 (1H, d, *J* 8.0, H-2), 6.73 (1H, d, *J* 8.0, H-3), 7.63 (1H, s, H-5), 8.80 (1H, s, H-8), and 12.00 (1H, s, D$_2$O exchangeable,

6-OH). δ_C 11.9, 17.6, 27.3, 41.9 (2'-3'-oxapentyl side chain), 100.6 (C-2)[a], 107.1 (C-3)[a], 107.8 (C-5)[a], 119.8 (C-4a)[b], 119.9 (C-8a)[b], 126.8 (C-8), 131.6 (C-7), 148.2 (C-1)[c], 150.5 (C-4)[c], 158.5 (C-6), 211.5 (C═O of 2′-3′-oxapentyl side chain). (Found: C, 70.5; H, 7.2%; HRMS: 288.1346. Calc. for $C_{17}H_{20}O_4$: C, 70.8; H, 7.0%; HRMS, 288.1362.)

Further elution afforded naphthol **12** (81 mg; 40%) identical in all respects to material synthesized earlier. Continued elution afforded boronic acid **27** (99 mg; 29%) as yellow-brown crystals, mp 211–213°C (from EtOAc–hexane); ν_{max} 3411 and 1627 cm^{-1}; δ_H 1.33 (6H, t, *J* 7.0, CH_3CH_2-), 3.58 (4H, q, *J* 7.0, CH_3CH_2-), 3.93 (6H, s, OCH_3), 6.53 (1H, d, *J* 7.0, H-2) 6.70 (1H, d, *J* 7.0, H-3), 7.50 [1H, s, D_2O exchangeable OH of $B(OH)_2$], 7.67 (1H, s, H-5), 8.23 (1H, s, H-8), and 9.30 [1H, s, D_2O exchangeable OH of $B(OH)_2$]. δ_C 13.5 and 42.6 (CH_3CH_2- respectively), 55.8 and 56.0 (OCH_3), 101.0 (C-2)[a], 105.5 (C-3)[a], 107.2 (C-5), 119.7 (C-4a)[b], 120.0 (C-8a)[b], 122.5 (C-8)[c], 129.0 (C-7)[c], 148.5 (C-1)[d], 150.1 (C-4)[d], 155.6 (C-6), 171.5 (C═O of the carbamate). Found: C, 58.6; H, 6.2%; HRMS 347.1544. Calc. for $C_{17}H_{22}BNO_6$: C, 58.8; H, 6.4%; HRMS: 347.1540.

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REFERENCES

1. Adeniyi, B. A.; Fong, H. H. S.; Pezzuto, J. M.; Lyengi, L.; Odelola, H. A. Antibacterial activity of diospyrin, isodiospyrin and bisdisodiospyrin from the root *Diospyros piscatonia* (Gurke) (Ebenaceae). *Phytother. Res.* **2000**, *14*, 112–117.
2. Ravishankara, M. N.; Shrivastava, N.; Jayathirtha, M. G.; Padh, H.; Rajani, M. Sensitive high-performance thin-layer chromatographic method for the estimation of diospyrin, a tumour inhibitory agent from the stem bark of *Diospyros Montana* Roxb. J. *Chromatogr. B* **2000**, 257–262.
3. Thompson, R. H. *Naturally Occurring Quinones III*: *Recent Advances, 3rd edition*; London: Chapman and Hall, 1987.
4. Lall, N.; Sarma, M. D.; Hazra, B.; Meyer, J. J. M. Antimycobacterial activity of diospyrin derivatives and a structural analogue of diospyrin against *Mycobacterium tuberculosis* in vitro. *J. Antimicrobial Chemother.* **2003**, *51*, 435–438.
5. Yoshida, M.; Mori, K. Synthesis of diospyrin, a potential agent against leishmaniasis related parasitic protozoan diseases. *Eur. J. Chem.* **2000**, 1313–1317.
6. Okamoto, I.; Doi, H.; Kotani, E.; Takeya, T. The aryl-aryl coupling reaction of 1-naphthol with $SnCl_4$ for 2,2'-binaphthol synthesis and its application to the biomimetic synthesis of binaphthoquinones isolated from *Plumbago zeylanica*. *Tetrahedron Lett.* **2001**, *42*, 2987–2989.

7. Danishefsky, S.; Kitahara, T.; Yan, C. F.; Morris, J. Diels–Alder reactions of *trans*-1-methoxy-3-trimethylsilyloxy-1,3-butadiene. *J. Amer. Chem. Soc.* **1979**, *101*, 6996–7000.
8. Sweeny, J. G.; Estrada-Valdes, M. C.; Iacobucci, G. A.; Sato, H.; Sakamura, S. Photoprotection of the red pigments of *Monascus anka* in aqueous media by 1,4,6-trihydroxynaphthalene. *J. Agri. Food. Chem.* **1981**, *29*, 1189–1193.
9. Ross Kelly, T.; Perekh, N. D. Regiochemical control in the Diels–Alder reaction of substituted naphthoquinones: The directing effects of C-6 oxygen substituents. *J. Org. Chem.* **1982**, *47*, 5009–5013.
10. Jung, M. E.; Hagenah, J. A. Synthetic approach to aklavanone using 2-oxo-2*H*-pyran-5-carboxylate (coumalate) intermediates. *J. Org. Chem.* **1987**, *52*, 1889–1902.
11. Giles, R. G. F.; Green, I. R. Autoxidation of some tetralin and tetralone derivatives under basic conditions. *S. Afr. J. Chem.* **1990**, *43*, 91–95.
12. AggarwalR.; Giles, R. G. F.; Green, I. R.; Oosthuizen, F. J.; Taylor, C. P. Synthesis in enantiopure form of four diastereoisomeric naphthopyranquinones derived from aphid insect pigments. *Org. Biomol. Chem.* **2005**, *3*, 263–273.
13. Sharp, M. J.; Snieckus, V. Synthetic connections to the aromatic directed metallation reaction. Unsymmetrical biaryls by Pd-catalysed cross coupling of directed by metallation derived arylboronic acids with aryl halides. *Tetrahedron Lett.* **1985**, *26*, 5997–6000.
14. Snieckus, V. Directed ortho metallation: Tertiary amide and *O*-carbamate directors in synthetic strategies for polysubstituted aromatics. *Chem. Rev.* **1990**, *90*, 879–933.
15. Lustig, E.; Benson, W. R.; Duy, N. Hindered-rotation in *N,N*-dimethylcarbamates. *J. Org. Chem.* **1967**, *32*, 851–852.